EXHIBIT C

Modafinil Improves Recovery After General Anesthesia

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Recovery from general anesthesia often involves residual sedation, drowsiness, fatigue, and lack of energy that may last hours to days. Modafinil is a wakefulness-promoting drug approved for patients with excessive daytime sleepiness associated with narcolepsy. We evaluated the effect of single doses of modafinil (200 mg) and placebo in patients recovering from general anesthesia. Thirty-four subjects participated in this prospective, randomized, double-blind study approved by our IRB. Preoperatively, patients were asked to rate various symptoms they had experienced over the previous 24-h using a verbal analog scale (VAS) of 0 to 10 as well as discrete scale when indicated. Postoperatively, once the patient was able to tolerate oral intake and met our institutional discharge criteria, the study drug (modafinil 200 mg or placebo) was administered with a sip of water. Patients were contacted 24 (1) hours after dosing to evaluate postdischarge symptoms. Patients in the placebo group reported significantly more postoperative fatigue (4.8 [3.3] versus 1.4 [1.8]), exhaustion (4.3 [3.3] versus 2.4 [3.1]), or degree of feeling worn out (4.7 [3.6] versus 2.9 [2.4]). Significantly more patients reported moderate to severe fatigue in the placebo group (65% versus 12%). Two major themes of "alertness" and "energy" were expressed by 71% of the patients receiving modafinil versus 18% of those receiving placebo. Patients recovering from general anesthesia can significantly benefit from modafinil.

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The trend continues toward providing more surgical services on an outpatient basis. More than 2/3 of patients receiving general anesthesia are for same-day discharge (1). Significant emphasis is placed on minimizing postoperative symptoms and facilitation of early discharge. Basic criteria for discharge include stability of vital signs (including pain) within an acceptable range, ability to tolerate liquid, acceptable degrees of nausea, and the ability to maintain an upright position without orthostasis (1). Further recovery is expected to take place after discharge. Although it is important to emphasize home readiness, recovery from anesthesia is not complete until the patient has returned to his/her preoperative status (1). Recovery from anesthesia and surgery can be associated with residual sedation, pain, nausea, and vomiting (1,2). Relatively few studies have evaluated recovery after discharge and they suffer from partial reporting and nonuniformity of data collection techniques. The overall incidence of postdischarge symptoms in outpatients is reported to be approximately 45% for pain, 42% for drowsiness, 21% for fatigue, 18% for dizziness, 17% for nausea, and 8% for vomiting (3). Approximately 14% of outpatients experience these symptoms for 3 or more days (2), and 62% require an average of 3.2 postoperative days to resume activities of daily living because of persistence of symptoms (3). These statistics do not describe the severity of symptoms.

Modafinil (Provigil®, Cephalon Inc., West Chester, PA) is a wakefulness-promoting drug approved by the Food and Drug Administration for patients with excessive daytime sleepiness associated with narcolepsy (4). The precise mechanism(s) through which modafinil promotes wakefulness is unknown. Modafinil is chemically unrelated to central nervous system stimulants (e.g., amphetamines, methylphenidate) and has a pharmacological profile different than that of sympathomimetic amines (4). During clinical trials, modafinil (200 mg/day and 400 mg/day) was shown to significantly improve daytime wakefulness without affecting nighttime sleep (4). In addition, modafinil has been shown to reduce fatigue and confusion in sleep-deprived pilots (5). Some of modafinil's effects appear to be opposite of those seen in patients recovering from general anesthesia (i.e., feeling tired, sleepy, and dizzy). We hypothesized that modafinil,

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by reducing fatigue and improving alertness, would improve recovery after general anesthesia.

The primary objective of this investigation was to evaluate the effect of modafinil on the degree of fatigue and drowsiness in patients after general anesthesia. Secondary objectives included evaluation of the effect of modafinil on recovery of cognition as well as subject-reported indicators of behavioral and somatic functions.

Methods

Informed consent was obtained from patients scheduled to undergo outpatient surgical procedures under general anesthesia to participate in this prospective study approved by our IRB. This study consisted of two parts. In the first part, patients were studied to pilot-test a questionnaire developed for this study to make certain that patients understood the questions (Appendix). The second objective of the pilot study was to obtain our own baseline data due to the limitations of reported incidences of postdischarge symptoms. The second part was a random design, double-blind, placebo controlled study to evaluate the effect of a single 200 mg dose of modafinil on recovery variables after general anesthesia.

Study 1: Symptom Incidence Evaluation, Open Label Study

Thirty-three subjects of either gender, between the ages of 18–65 yr, participated in this open label study. Subjects were ASA physical status I–II, with a body mass index <40 without any known significant renal, hepatic, cardiovascular, neurological, gastrointestinal, endocrine, hematologic, or pulmonary diseases as judged by the investigator. A history of epilepsy, alcoholism, or chronic use of opioids also excluded the subjects from participation in this study. In our institution patients scheduled for outpatient surgery usually arrive 2 h prior to their scheduled surgery. After surgery, assuming no complications, patients remain in the postanesthesia care unit (PACU) for about 1 h and are transferred to a phase II recovery unit and discharged approximately 30 min later. Preoperatively (within 1–2 h prior to their scheduled surgery) patients were asked to rate various symptoms they had experienced over the previous 24-h using a verbal analog score (VAS) rating from 0 to 10, as well as discrete scores when indicated (Appendix). Postoperatively patients were monitored, cared for, and discharged according to our institutional standards. Anesthetic management of the patient was at the discretion of the attending anesthesiologist; it was assumed that patients are at similar stages of recovery when discharged from the hospital. The same questions were asked 24 (±1) h postdischarge via a phone call (Appendix). Subjects were also asked to rate their satisfaction with recovery from general anesthesia. Subjects in part one of the study did not receive placebo.

Study 2: Treatment Evaluation

Thirty-four subjects scheduled for same day surgery under general anesthesia participated in this study. This was a randomized, prospective, double-blind, parallel group study. Subjects in this group had the same inclusion/exclusion criteria as the first study and answered the preoperative questionnaire 1–2 h before their scheduled surgery. Anesthetic management of these patients was also at the discretion of the attending anesthesiologist. Once the patient was able to tolerate oral intake and met our institutional discharge criteria, the study drug (Provigil® 200 mg] or placebo was administered, randomly, with a sip of water. Patients were contacted 24 (±1) h after dosing for symptom evaluations. Postoperatively, these patients were also asked whether the study drug they received (placebo or modafinil) had any beneficial effect. If the patient felt they received a benefit from the study drug they were asked to describe the benefit in their own words.

Data were analyzed using paired and unpaired Student's *t*-test, χ^2 statistics, content analysis, 95% confidence interval, and power analysis. Data are reported as mean (± SD). A $P < 0.05$ was considered statistically significant.

Results

Study 1

Thirty-three subjects (7 male, 26 female) with a mean age of 40 (11) years and a mean weight of 175 (45) lb participated in Study 1. Table 1 depicts the pre- and postoperative variables in these patients. Postoperatively, subjects had significantly more nausea (6% versus 27% reported having at least a mild degree of nausea [VAS ≥ 3]), were significantly more dizzy (0% versus 52% reported having at least a mild degree of dizziness [VAS ≥ 3]), had significantly less appetite (12% versus 36% reported having at least a moderate degree of reduced appetite [VAS ≤ 5]), had significantly more pain (9% versus 48% reported having at least a moderate degree of pain [VAS ≥ 5]), were significantly less tense (36% versus 15% reported having at least a moderate degree of being tense [VAS ≥ 5]), were significantly more worn out (15% versus 52% reported having at least a moderate degree of being worn out [VAS ≥ 5]), were significantly more fatigued (18% versus 75% reported having at least a moderate degree of fatigue [VAS ≥ 5]), and were significantly more exhausted (30% versus 73% reported having at least a moderate degree of exhaustion [VAS ≥ 5]). Subjects reported having significantly less energy but were more relaxed postoperatively. The majority of

Table 1. Reported Verbal Score for Experienced Variables During the First 24 Hours Postdischarge in the Open Label Study

Variables	Preoperative	Postoperative
Energy	6.8 (2.4)	3.9 (2.7)*
Appetite	8.0 (2.5)	5.7 (3.4)*
Nausea	1.1 (2.1)	3.3 (4.0)*
Restless	4.4 (3.4)	3.7 (4.1)
Tense	4.6 (3.7)	2.0 (3.1)*
Worn out	3.4 (2.9)	6.3 (3.3)*
Fatigue	3.5 (3.0)	5.6 (3.1)*
Exhaustion	2.9 (3.1)	5.6 (3.5)*
Relaxed	4.4 (2.6)	7.9 (2.3)*
Dizziness	0.3 (0.84)	3.0 (3.2)*
Reading ability	9.2 (0.4)	8.2 (2.6)
Pain	2.0 (2.7)	5.4 (2.8)*
Ease of sleep	7.1 (2.3)	6.5 (2.6)
Mental limitation to resume activity	—	1.7 (2.7)

Values are mean (SD); $n = 33$.
* Significantly different from preoperative value, $P < 0.01$.

subjects complained of symptoms representing inadequate recovery. However, overall satisfaction with recovery from anesthesia was very high (9.4 [0.96]).

Study 2

Thirty-four subjects (24 female, 10 male, $n = 17$ per group) participated in this study. Table 2 summarizes the data between these 2 groups. There were no significant differences in age, height, weight, or gender distribution between the 2 groups (Table 2). Almost all had received the same type of anesthetic management, which included propofol, a narcotic, a volatile drug, a muscle relaxant, nitrous oxide, and oxygen. Subjects had undergone mostly orthopedic or gynecological surgical procedures. Surgical procedures or the exact doses of anesthetics were not compared between the groups.

Table 3 compares the variables between modafinil and placebo groups. There were no significant differences in preoperative symptoms between the 2 groups. As expected, patients were more tense, more restless, and less relaxed preoperatively (in both groups).

Postdischarge symptoms in patients receiving placebo were 12% for dizziness (VAS $\geq$ 3), 35% for nausea (VAS $\geq$ 3), 65% for feeling worn out (VAS $\geq$ 5), and 76% for pain (VAS $\geq$ 5). Postdischarge symptoms in the modafinil group were 12% for dizziness, 23% for nausea, 29% for feeling worn out, and 53% for pain. Patients receiving placebo reported significantly more postoperative fatigue, exhaustion, or degree of feeling worn out (Table 3). Significantly more patients reported moderate to severe fatigue (VAS $\geq$ 5) in the placebo group (65% versus 12%, 86% power using a two-sided χ^2 test with continuity correction and an α level of 0.05). Significantly more patients in the placebo group reported moderate to severe (VAS $\geq$ 5) degree of feeling worn out (65% versus 29%). The incidence of moderate to severe exhaustion was the same in the modafinil (24%) or placebo group (29%).

Table 2. Demographic Data

	Modafinil	Placebo
Age (yr)	42 (10)	41 (12)
Weight (lb)	176 (33)	178 (39)
Height (in)	65 (3.2)	67 (3.4)
Gender (M/F)	4/13	6/11

Patients receiving placebo were sleepier and admitted to more episodes of napping after discharge to home; these patients also had more difficulty remaining asleep during the first night after discharge.

We defined postoperative distress as lack of energy, a presence of feeling worn out, fatigued, exhaustion, mental clouding, and problems with reading (comprehension) (total of 60 possible points). In the modafinil group, this value was 10.5 (6.0) preoperatively and increased to 11.3 (9.1) postoperatively. The corresponding values on the placebo group were 13.4 (11.9) and 21.0 (13.8), respectively. Patients receiving modafinil had significantly less postoperative distress than those receiving placebo.

Patients were asked to describe if the study drug benefited them. Content analysis of the comments made by the patients receiving modafinil revealed two major themes of "alertness" and "energy" expressed by 71% of the patients. Being "alert" was indicated by almost half of these patients. Typical statements were as follows: "felt real alert," "not groggy," "more alert than the last time." Being energetic was indicated by another half. Typical statements are as follows: "did not feel tired," "more energy than past surgery." Such statements were expressed by 18% of patients in the placebo group. The difference in proportions is both clinically and statistically significant (84% power using a two-sided χ^2 test with continuity correction and an α level of 0.05).

Two patients in the modafinil group complained of restlessness. Four patients in the placebo group and one patient in the modafinil group complained of not being able to fall asleep at night; these patients had naps of a few hours after going home.

Discussion

The results of this study demonstrate that, compared to placebo, modafinil significantly hastens recovery from residual anesthetic effects and improves feelings of alertness and energy in postoperative patients. Patients recovering from general anesthesia can significantly benefit from modafinil administration.

Recovery from anesthesia is a time-dependent process. Depending on the definition, recovery from anesthesia may last days in a given patient. Most emphasis on recovery from anesthesia during the

Table 3. Reported Verbal Score for Experienced Variables During the First 24 Hours Postdischarge in the Modafinil and Placebo Groups

Variables	Modafinil	Placebo
Energy		
Preoperative	7.5 (2.8)	6.8 (2.8)
Postoperative	6.2 (3.5)	5.2 (2.7)
Difference	−1.3	−1.6
Appetite		
Preoperative	7.9 (2.9)	6.4 (3.4)
Postoperative	6.1 (3.8)	6.8 (3.2)
Difference	−1.8	+0.4
Nausea		
Preoperative	0.6 (2.4)	1.0 (1.7)
Postoperative	1.9 (3.5)	2.2 (3.3)
Difference	+1.3	+1.2
Restless		
Preoperative	4.5 (3.7)	3.4 (3.6)
Postoperative	2.5 (3.0)	3.4 (3.1)
Difference	−2.0	0.0
Tense		
Preoperative	5.4 (3.6)	4.0 (3.2)
Postoperative	2.2 (3.2)	1.1 (2.1)
Difference	−3.2	−2.9
Worn Out		
Preoperative	3.5 (3.4)	2.5 (2.9)
Postoperative	2.9 (2.4)	4.7 (3.6)†
Difference	−0.6	+2.2
Fatigue		
Preoperative	1.6 (2.7)	2.8 (3.0)
Postoperative	1.4 (1.8)	4.8 (3.3)*
Difference	−0.2	+2.0
Exhaustion		
Preoperative	2.2 (3.3)	2.3 (3.0)
Postoperative	2.4 (3.1)	4.3 (3.3)†
Difference	+0.2	+2.0
Ease of Sleep		
Preoperative	6.5 (3.3)	6.4 (3.3)
Postoperative	6.2 (3.6)	6.6 (0.9)
Difference	−0.3	+0.2
Dizziness		
Preoperative	0.0	0.17 (0.12)
Postoperative	0.83 (1.3)	0.76 (1.1)
Difference	+0.83	+0.59
Relaxed		
Preoperative	5.1 (3.5)	5.7 (3.2)
Postoperative	7.4 (3.3)	8.2 (2.0)
Difference	+2.3	+2.5
Pain		
Preoperative	1.9 (2.8)	2.7 (2.1)
Postoperative	5.4 (3.2)	6.1 (2.2)
Difference	+3.5	+3.4
Reading Ability		
Preoperative	9.0 (2.1)	8.6 (1.9)
Postoperative	9.2 (1.6)	7.5 (3.6)
Difference	+0.2	−1.1
Mental Limitation to Resume Activity		
Postoperative	0.6 (1.6)	1.5 (2.2)

Values are mean (SD); $n = 17$ in each group.
* $P < 0.05$ between the two groups; † $P < 0.01$ between the two groups.

past 2 decades has been placed on facilitating patient discharge to reduce cost (1). Many clinicians expect further recovery to occur after discharge. Current discharge criteria include stability of vital signs within an acceptable range, no excessive pain requiring parenteral therapy, toleration of oral liquid, minimal nausea and vomiting, ability to stand up without orthostasis, and the presence of a responsible adult to escort the patient home (1). The emphasis on recovery from anesthesia in the current medical climate is on home readiness to reduce medical expenses (1,3). Very little is known about the presence of postdischarge symptoms. The reported studies suffer from partial reporting, as well as heterogeneity in symptom definition and methods of evaluation (1,3). It is generally known that most patients are very satisfied with their recovery from anesthesia. Because satisfaction is influenced by factors not related to recovery (i.e., expectation and relationship with the caregiver) it should not be used as the sole indicator of recovery from anesthesia. In addition, the only significant postdischarge symptoms should not be those resulting in patient readmission.

The overall incidences of these symptoms is reported to be approximately 45% for pain, 42% for drowsiness, 21% for fatigue, 18% for dizziness, 17% for nausea and 8% for vomiting (3). The above statistics, however, do not describe severity. In Study 1 (open label study), many patients complained of postdischarge symptoms representing inadequate recovery from anesthesia. Many patients had significant dizziness, moderate to severe pain, or moderate to severe postoperative fatigue. In Study 2 subjects receiving modafinil reported significantly less frequent incidences of feeling worn out, and moderate to severe fatigue. The incidence of moderate to severe exhaustion was the same in the modafinil or placebo group. Patients receiving placebo were sleepier and admitted to more episodes of napping after discharge to home; these patients also had more difficulty remaining asleep during the first night after discharge.

A few issues need to be discussed regarding our methodology. First, the anesthetic management of our subjects was not standardized because it was assumed that patients are at very similar degree of recovery before discharge from the hospital; small variations in recovery between subjects were expected to be controlled by random assignment of subjects to the two experimental groups. We did not compare time from the end of anesthesia until the administration of study drug because all patients were dosed within 2–3 hours of arrival in the PACU. Patient discharge from PACU can be influenced by factors not related to recovery from anesthesia. Furthermore, the design of our study more closely resembles routine clinical practice. The dose of modafinil selected was based on the fact that the usual daily dose of modafinil is 200 mg. Finally, this was a "proof of concept" study and, therefore, limited in scope.

Findings of most studies generally suggest that patients recovering from general anesthesia often complain of residual sedation, fatigue, pain, and a general feeling of being down. In patients recovering from general anesthesia, modafinil significantly reduces the degree of fatigue, incidence of moderate to severe fatigue, and postoperative distress (as defined above). In addition, modafinil significantly improves feelings of alertness and energy in patients recovering from general anesthesia. Modafinil may share the same pathways, or receptors, as sedatives, hypnotics, or general anesthetics to produce its effect(s). Patients recovering from general anesthesia can significantly benefit from modafinil. Multiple dosing may be needed in those patients who experience an exaggerated depressive response to anesthetics.

Appendix. Questionnaire

1) How much headache did you have during the past 24 hours?___
0 is no headache at all
10 is the WORST headache
2) How much dizziness did you have during the past 24 hours?___
0 is no dizziness at all
10 is extremely dizzy
3) How much energy did you have during the past 24 hours?___
0 is no energy at all
10 is normal level of energy
4) How was your appetite during the past 24 hours?___
0 is no appetite at all
10 is normal appetite
5) How nauseated were you during the past 24 hours?___
0 is no nausea at all
10 is extremely nauseated
6) Did you have an episode of vomiting during the past 24 hours? Yes/No
How many episodes?___
What time of the day?___Am/pm
7) How tense have you been during the past 24 hours?___
0 is not tense at all
10 is extremely tense
8) How worn out have you been during the past 24 hours?___
0 is not worn out at all
10 is extremely worn out
9) How relaxed have you been during the past 24 hours?___
0 is not relaxed at all
10 is very relaxed
10) How restless have you been during the past 24 hours?___
0 is not restless at all
10 is extremely restless
11) How much fatigue did you have during the past 24 hours?___
0 is no fatigue at all
10 is extremely fatigued
12) How exhausted have you been during the past 24 hours?___
0 is not exhausted at all
10 is extremely exhausted
13) How much pain did you have during the past 24 hours?___
0 is no pain at all
10 is very severe pain
Was the pain incisional? yes/no
Please describe your pain in your own words. _______________
*14) Did you take any pain medication after leaving the hospital? Yes/No
What did you take?___
How many?___
15) How well did you sleep last night?___
0 is no sleep at all
10 is sound sleep
16) During the last 24 hours how able were you to read for business or pleasure?___
0 is not able at all
10 is very easy
*17) If it was not for any physical limitations did you feel that mentally you were able to resume your routine activities?___
0 is no mental limitation
10 is completely limited mentally
**18) Do you think the study drug benefited you? Yes No
If yes in what ways?________

* This question was asked postoperatively only. ** This question was asked postoperatively only in Study 2.

The direction of scoring of the items are not systematic to control for 'acquiescence response style'—(A tendency to constantly endorse one extreme end of the scale, always agree or disagree, "Yea-sayer" and Nay-sayer"), a common practice in test development. When appropriate, however, reverse scoring was used in data analysis.

References

1. Marshall SI, Chung F. Discharge criteria and complications after ambulatory surgery. Anesth Analg 1999;88:508–17.
2. Myles PS, Williams DL, Hendrata M, et al. Patient satisfaction after anesthesia and surgery: result of a prospective survey of 10811 patients. Br J Anaesth 2000;84:6–10.
3. Wu CL, Berenholtz SM, Pronovost PJ, Fleisher LA. Systematic review and analysis of postdischarge symptoms after outpatient surgery. Anesthesiology 2002;96:994–1003.
4. Provogil® (modafinil) [package insert]. West Chester, PA: Cephalon, Inc.; 1999.
5. Caldwell JA Jr, Caldwell JL, Smythe III NK, Hall KK. A double blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter simulator study. Psychopharmacology 2000;150:272–82.